THE REJECTION UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

The Examiner has rejected claims 1, 2, 5, and 7 under 35 U.S.C. § 102(b)[1] as being anticipated by da Costa *et al.*, 2000, Cancer Chemother. Pharmacol. 46 (Suppl.): S33-S36 ("da Costa"). Applicants respectfully disagree for the reasons discussed below.

First, Applicants note that claim 1 has been amended to clarify that claim 1 is directed to the treatment of Hodgkin's Disease using anti-CD30 antibodies that are themselves cytostatic or cytotoxic to Hodgkin's Disease cells in the absence of cell types other than the Hodgkin's Disease cells. In contrast, da Costa teaches combining two antibodies, one of which is HRS-3 (see Pohl *et al.*, 1993, Int. J. Cancer 54:820-27, reference BN of the Second Supplemental Information Disclosure Statement submitted herewith, at page 882, left column; see also da Costa at page 834, results section), an anti-CD30 antibody that in itself does not have anti-tumor activity against CD30-expressing cancers (see discussion of U.S. Patent No. 5,165,923 to Thorpe in the Amendment dated October 17, 2001) to form bispecific antibodies that cross link CD30-expressing cells with effector cells such as natural killer cells or T cells (see da Costa at page S34, Results section). It is the cross-linking of the CD30-expressing cells and the effector cells that results in effector cell-mediated killing of the CD30-expressing cells, not the binding of the CD30 bispecific antibodies. For example, da Costa states that, with respect to the CD16/CD30 bispecific antibody, the binding of the antibody to resting natural killer cells resulted in activation of the natural killer cells and destruction of the tumor cells (see da Costa at page S34, right column). Thus, the CD16/CD30 bispecific antibody "was able to retarget human NK cells toward $CD30^+$ target cells and induce their lysis" (see Abstract). Further, with respect to bispecific antibodies that cross-link T cells to Hodgkin's Disease cells, da Costa states that "bridging of Hodgkin tumor cells to T cell-triggering molecules with a combined α-CD30/CD3 and α-CD30/CD28 bi-mAb regimen induced tumor cell lysis in vitro and in vivo" (da Costa at page S35, left column). Thus, according to da Costa, a combination of co-T cell-stimulatory bispecific antibodies, namely a CD28/CD30 bispecific antibody and a CD3/CD30 bispecific antibody, was able to stimulate T-cell activation and induce Hodgkin tumor cell lysis by the T

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[1] Although the claims are rejected under 35 U.S.C. § 102(b), Applicants believe that the rejection was intended to be under 35 U.S.C. § 102(a), as da Costa was published in July 2000, approximately four months before the filing date of the instant application.

cells. This is stated more explicitly in an earlier paper by the same group, authored by Renner and Pfreundschuh, 1995, Immunol. Rev. 145:179-209 ("Renner"; reference BN of the second Supplemental Information Disclosure Statement submitted herewith), which states at page 192 that the "combination of CD33/CD30 and CD28/CD30 was cytotoxic [towards L540 Hodgkin's cells] only when [peripheral blood lymphocytes] were used that had been previously stimulated with the Bi-MAB CD3/CD30 in the presence of $CD30^+$ cells." (Emphasis added). In direct contrast, the presently claimed methods of claims 1-7 entail the use of antibodies, such as AC10 and HeFi-1, that exert a cytotoxic or cytostatic effect on Hodgkin's Disease cell lines in the absence of cells other than cells of the Hodgkin's Disease cell line, and thus in the absence of effector cells (see example in Section 6 of the specification at pages 50-51). Therefore, da Costa does not anticipate claim 1, nor does da Costa anticipate claims 2, 5 and 7 dependent thereon.

In view of the foregoing, Applicants submit that the rejection of claims 1, 2, 5 and 7 as anticipated by da Costa is in error and/or has been obviated by the present amendment and thus should be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 1-7 are rejected under 35 U.S.C. § 103(a), allegedly as being obvious over da Costa in view of Engert *et al.*, 1999, "Treatment of Advanced Hodgkin's Lymphoma: Standard and Experimental Approaches," Seminars in Hematology 36(3):282-289 ("Engert").[2] Applicants respectfully disagree for the reasons discussed below.

First, with respect to da Costa, Applicants reiterate that da Costa does not teach the use of an anti-CD30 antibody that is cytostatic or cytotoxic to Hodgkin's Disease cells in the absence of effector cells, as is claimed in claim 1 and claims 2-7 dependent thereon. Further, da Costa does not suggest the treatment of Hodgkin's Disease with an anti-CD30 antibody that in the absence of conjugation to a cytotoxic or cytostatic agent has cytotoxic or cytostatic properties against Hodgkin's Disease cells in the absence of other cells such as effector cells. Accordingly, da Costa does not render obvious the invention of claims 1-7.

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[2] Although the Office Action does not provide the full citation of the Engert reference, Applicants believe that Office Action refers to the same Engert reference relied upon by the Examiner in the Office Action dated July 18, 2001.

Engert does not remedy the deficiencies of da Costa. Engert discusses the use of chemotherapy for treatment of Hodgkin's Disease. Engert further discusses the use of immunotherapy, including immunotherapy with anti-CD30 antibody based immunotoxins, to treat Hodgkin's Disease. However, Engert does not teach or suggest the use of an anti-CD30 antibody to treat Hodgkin's Disease that is cytostatic or cytotoxic to Hodgkin's Disease cells without conjugation to a cytotoxic or cytostatic agent and without effector cells. Therefore, Engert, whether alone or in combination with da Costa, does not render obvious the presently claimed invention.

Applicants submit that the rejection of claims 1-7 under 35 U.S.C. § 103(a) is in error and respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the file history of the present application. In view of the amendments and remarks above, it is submitted that all the outstanding rejections have been overcome or obviated. Further, it is submitted that the claims are in form for allowance. If any issues remain, the Examiner is respectfully requested to telephone the undersigned at (212) 790-2247 to discuss any issues or questions.

Respectfully submitted,

Date: March 18, 2002

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Enclosures

Exhibit A
U.S. Application No. 09/724,406
Marked Up Version of Amended Paragraph in Specification

Marked up version of amended paragraph starting at page 51, line 16 of the specification:

In another set of experiments, HD cell lines were incubated with soluble AC10 or HeFi-1 that were cross-linked in solution by the addition of soluble goat anti-mouse IgG antibodies. Under these [cross-liking] cross-linking conditions, all four HD cell lines, when plated at $5x10^4$ cell/well, were growth inhibited by AC10 and HeFi-1 (FIG. 3). When the cells were plated at $5x10^3$ cell/well, all four HD cell lines were growth inhibited by AC10, while three of the four cell lines, HDLM-2, L540, and L428, were growth inhibited by HeFi-1 (FIG. 4).

Exhibit B
U.S. Application No. 09/724,406
Clean Version of Amended Paragraph in Specification

Clean version of amended paragraph starting at page 51, line 16 of the specification:

In another set of experiments, HD cell lines were incubated with soluble AC10 or HeFi-1 that were cross-linked in solution by the addition of soluble goat anti-mouse IgG antibodies. Under these cross-linking conditions, all four HD cell lines, when plated at $5x10^4$ cell/well, were growth inhibited by AC10 and HeFi-1 (FIG. 3). When the cells were plated at $5x10^3$ cell/well, all four HD cell lines were growth inhibited by AC10, while three of the four cell lines, HDLM-2, L540, and L428, were growth inhibited by HeFi-1 (FIG. 4).

Exhibit C
U.S. Application No. 09/724,406
Marked Up Version of Amended Claims

1. (Twice amended) A method for the treatment of Hodgkin's Disease in a subject comprising administering to the subject, in an amount effective for said treatment, (a) an antibody that (i) immunospecifically binds CD30 and (ii) exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line, wherein said antibody exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line in the absence of conjugation to a cytostatic or cytotoxic agent, respectively, and in the absence of cells other than cells of said Hodgkin's Disease cell line; and (b) a pharmaceutically acceptable carrier.

Exhibit D
U.S. Application No. 09/724,406
Claims as Pending Following Entry of Amendments Made Herein

1. (Twice amended) A method for the treatment of Hodgkin's Disease in a subject comprising administering to the subject, in an amount effective for said treatment, (a) an antibody that (i) immunospecifically binds CD30 and (ii) exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line, wherein said antibody exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line in the absence of conjugation to a cytostatic or cytotoxic agent, respectively, and in the absence of cells other than cells of said Hodgkin's Disease cell line; and (b) a pharmaceutically acceptable carrier.

2. The method of claim 1, wherein the antibody is human, humanized or chimeric.

3. The method of claim 1, further comprising administering chemotherapy to said subject.

4. The method of claim 1, wherein the antibody is conjugated to a cytotoxic agent.

5. The method of claim 1, wherein the antibody is a fusion protein comprising the amino acid sequence of a second protein that is not an antibody.

6. The method of claim 4 or 5, further comprising administering chemotherapy to said subject.

7. (Amended) The method of claim 1, wherein the cytostatic or cytotoxic effect is exhibited upon performing a method comprising:

(a) contacting a culture of the Hodgkin's Disease cell line with the antibody, said culture being of about 5,000 cells in a culture area of about 0.33 cm^2, said contacting being for a period of 72 hours;

(b) exposing the culture to 0.5 μCi of ^{3}H-thymidine during the final 8 hours of said 72-hour period; and

(c) measuring the incorporation of ^{3}H-thymidine into cells of the culture,

wherein the antibody has a cytostatic or cytotoxic effect on the Hodgkin's Disease cell line if the cells of the culture have reduced ^{3}H-thymidine incorporation compared to cells of the same Hodgkin's Disease cell line cultured under the same conditions but not contacted with the antibody.

8. (Amended) A method for the treatment of Hodgkin's Disease in a subject comprising administering to the subject an amount of a protein, which protein (a) competes for binding to CD30 with monoclonal antibody AC10 or HeFi-1, and (b) exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line, which amount is effective for the treatment of Hodgkin's Disease.

11. (Amended) A method for the treatment of Hodgkin's Disease in a subject comprising administering to the subject an amount of a protein, which protein (a) comprises an amino acid sequence that has at least 95% identity to SEQ ID NO:2 or SEQ ID NO:10, and (b) immunospecifically binds CD30, which amount is effective for the treatment of Hodgkin's Disease.

13. (Amended) The method of any one of claims 8 or 11, wherein the protein is a human, humanized or chimeric antibody.

14. (Amended) The method of any one of claims 8 or 11, further comprising administering chemotherapy to said subject.

15. (Amended) The method of any one of claims 8 or 11, wherein the protein is conjugated to a cytotoxic agent.

16. (Amended) The method of any one of claims 8 or 11, wherein the protein is a fusion protein comprising the amino acid sequence of a second protein.

17. The method of claim 15, further comprising administering chemotherapy to the subject.

18. The method of claim16, further comprising administering chemotherapy to the subject.

19. (Amended) The method of any one of claims 8 or 11, wherein the cytostatic or cytotoxic effect is exhibited upon performing a method comprising:

(a) contacting a culture of the Hodgkin's Disease cell line with the protein, said culture being of about 5,000 cells in a culture area of about 0.33 cm^2, said contacting being for a period of 72 hours;

(b) exposing the culture to 0.5 μCi of ^{3}H-thymidine during the final 8 hours of said 72-hour period; and

(c) measuring the incorporation of ^{3}H-thymidine into cells of the culture,

wherein the protein has a cytostatic or cytotoxic effect on the Hodgkin's Disease cell line if the cells of the culture have reduced ^{3}H-thymidine incorporation compared to cells of the same Hodgkin's Disease cell line cultured under the same conditions but not contacted with the protein.